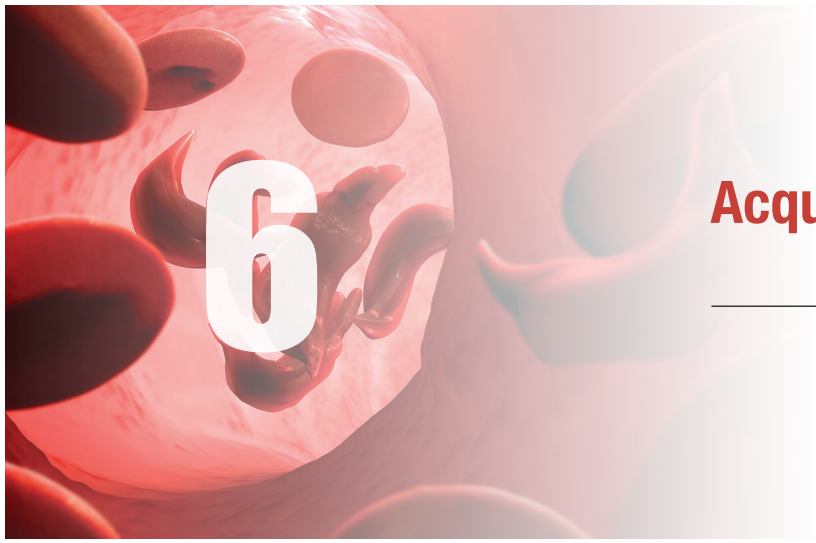

6 Acquired underproduction anemias

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Introduction

We define underproduction anemias clinically by the presence of anemia and a corrected reticulocyte count [(reticulocyte percent × patient's hematocrit)/normal hematocrit] of approximately <2%, which indicates an inappropriately low response by the marrow to the degree of anemia. The acquired and congenital (reviewed elsewhere) underproduction anemias can be further grouped by red blood cell (RBC) size—that is, mean corpuscular volume (MCV)—into microcytic (eg, iron deficiency anemia [IDA], thalassemia), normocytic (eg, anemia of inflammation, anemia associated with chronic kidney disease [CKD]), and macrocytic (eg, megaloblastic anemias, acquired pure red cell aplasia [PRCA], and myelodysplastic syndromes [MDSs]). The normal ranges of MCV vary by age and gender. A number of other acquired anemias with low corrected reticulocyte counts are not routinely categorized by cell size but are often normocytic. These conditions can be complicated by multiple pathophysiologies that suppress RBC production and are discussed in separate sections within this chapter (ie, "Anemia of cancer," "Myelophthisic anemia," "Anemia of malnutrition," "Anemias associated with endocrine disorders and pregnancy," "Anemia in older persons," and "Anemia associated with HIV infection"). This chapter focuses only on the acquired underproduction anemias (see Chapter 15 for congenital underproduction anemias). A variety of primary hematopoietic disorders can affect the bone marrow and lead to acquired underproduction anemia as well other cytopenias. Detailed discussion of these entities is included elsewhere (eg, aplastic anemia, acute leukemia, and MDS). An outline of the acquired underproduction anemias covered in this chapter is depicted in Table 6-1.

Overview of erythropoiesis

Erythropoiesis is the process by which hematopoietic stem cells divide, differentiate, and mature into enucleated RBCs. The earliest identifiable erythroid progenitor is the burst-forming unit-erythroid, which is defined functionally by its ability in vitro to form large "bursts" of erythroblast colonies of various sizes after approximately 2 weeks in semisolid media. Each burst-forming unit-erythroid can generate between 1000 to 10,000 erythroblasts. The next defined stage is the colony-forming unit-erythroid (CFU-E), which under low concentrations of erythropoietin (EPO) give rise to 100 to 200 well-hemoglobinized

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Table 6-1 Selected acquired underproduction anemias reviewed in this chapter

Microcytic*	Iron deficiency anemia
Normocytic	Anemia of inflammation (~30% are microcytic)
	Anemia associated with chronic kidney disease
Macrocytic	Megaloblastic anemia (vitamin B_{12} and folate deficiencies)
	Acquired pure red cell aplasia
	Anemia associated with liver disease
	Acquired sideroblastic anemias (often macrocytic)†
Other	Anemia of cancer
	Myelophthisic anemias
	Anemia from malnutrition/anorexia nervosa
	Anemia associated with endocrine disorders
	Anemia associated with pregnancy
	Anemia of older patients
	Anemia associated with HIV infection

*If we consider all underproduction microcytic anemias (not just those that are acquired), one can think of these broadly as caused by heme (iron, many congenital sideroblastic anemias) or globin (thalassemia) deficiency.

†Many (but not all) congenital sideroblastic anemias are microcytic.

erythroblasts after approximately 1 week in culture. The erythroid stages subsequent to CFU-E (proerythroblast to basophilic erythroblast to polychromatic to orthochromatic erythroblast) are defined by their light microscopic appearance on marrow aspirate slides. The pyknotic erythroblast (nucleated red blood cell) undergoes enucleation to produce a reticulocyte, which spends 1 to 2 days in the marrow followed by 1 to 2 days in the peripheral blood, in which the RNA is completely lost and the mitochondria are degraded and the mature red cell results. EPO is the primary cytokine that controls erythropoiesis and acts on erythroid progenitors in the stages of CFU-E to the earliest basophilic erythroblasts. It takes approximately 7 days for a CFU-E to differentiate into a reticulocyte, and, clinically, this corresponds to the absolute reticulocyte count increase of approximately 7 days after EPO signaling (eg, following acute hemorrhage). Further information on EPO is provided in Chapter 4.

Heme is a complex of ferrous iron and protoporphyrin IX (PPIX). There are 8 enzymes in the mammalian heme synthetic pathway (Figure 6-1). The first step occurs within the mitochondria where 5-aminolevulinate synthase (ALA-S2), along with vitamin B_6, catalyzes the condensation of glycine and succinyl coenzyme A (CoA) to yield δ-aminolevulinic acid (ALA). This is the rate-limiting step in heme production and is regulated by iron availability in erythroid cells. ALA is transported to the cytosol, where 4 additional enzymatic reactions occur, producing coproporphyrinogen III (Copro III), which is transported back into the mitochondria for the remaining 3 steps in the pathway. The final step, catalyzed by the enzyme ferrochelatase (FECH), incorporates iron into PPIX.

In adults, approximately 200 billion erythrocytes are produced each day to replace senescent red cells that are removed from circulation. This requires bone marrow stem cells, iron, cytokines (including EPO), vitamins, and a suitable marrow microenvironment. Deficiency or unavailability of any of these key components results in decreased RBC production and anemia.

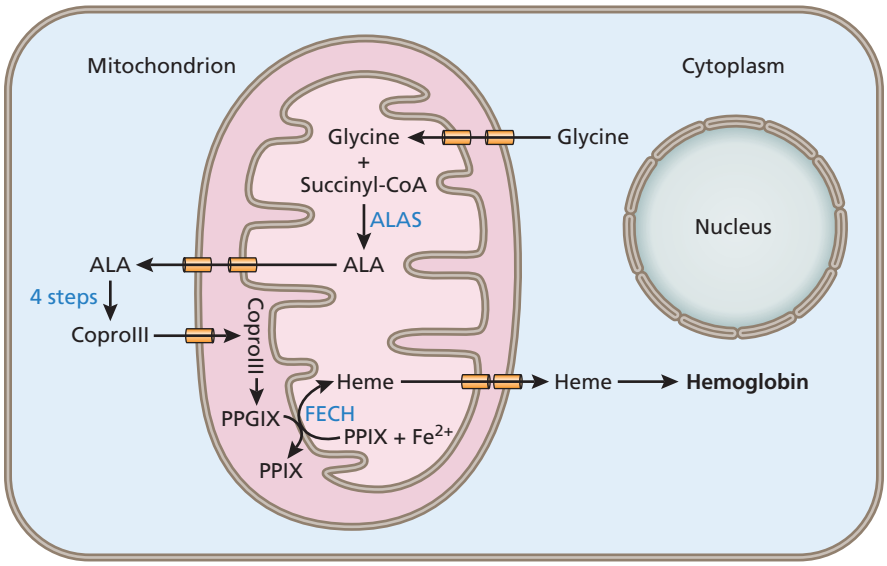

Figure 6-1 Heme synthesis. ALAS, 5-aminolevulinate synthase; PPGIX, protoporphyrinogen IX.

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Microcytic anemias

Iron deficiency anemia

CLINICAL CASE

A 38-year-old woman presents to her gynecologist complaining of prolonged heavy menstrual bleeding with resultant dyspnea on exertion and fatigue. Laboratory evaluation reveals a microcytic anemia with a hemoglobin of 6.8 g/dL, MCV of 68 fL, and reticulocyte count of 1%. White blood cell count is normal, and the platelet count is slightly elevated at 502,000/mL. Iron studies reveal a low serum iron, elevated total iron-binding capacity (TIBC), and a markedly reduced ferritin of 5 µg/L. A workup identifies endometrial fibroids. Intravenous iron therapy is administered with good clinical response.

Background

Iron deficiency (defined by a low serum ferritin) is the most common cause of anemia worldwide, affecting over 1 billion people, predominantly women and children. Data from the US National Health and Nutrition Examination Survey (NHANES) from 2003 to 2010 found that iron deficiency affected approximately 15% of toddlers, 11% of nonpregnant adolescent girls, and 9% of adult women (aged 20 to 49 years).

Iron recycling and dietary iron intake

The vast majority of the body's iron is contained in hemoglobin within erythroid cells, of which approximately 25 mg is efficiently recycled each day. Senescent RBCs are phagocytosed by reticuloendothelial macrophages, which degrade hemoglobin and export the released iron into the plasma where it binds transferrin. Transferrin-bound iron is then delivered to the bone marrow to support new RBC production or to the liver for storage as ferritin (~1 g in men and ~300 to 600 mg in menstruating women) or other sites. One to two milligrams of new iron enters the body each day from dietary intake and absorption, to replace that same amount of iron lost daily via normal sloughing of skin and intestinal cells.

Intestinal iron absorption depends on dietary iron amount, bioavailability, and physiological requirements. A typical Western diet contains approximately 10 to 20 mg of iron (roughly 6 mg of iron per 1000 calories), mostly as inorganic iron (cereals and legumes) and heme iron (red meats, fish, and poultry). Inorganic iron is absorbed less readily than heme iron. In iron-replete patients, approximately 10% of inorganic iron versus 30% of heme iron is absorbed. Reviewing the iron content of foods, as well as forms of iron consumed and foods and drinks that affect iron absorption (Tables 6-2 and 6-3), is useful when providing dietary counseling to iron-deficient patients. Such counseling is especially helpful for patients following restricted (vegetarian or vegan) diets. Further details on iron homeostasis, including regulation iron absorption, are provided in Chapter 5.

Table 6-2 Factors that affect dietary iron absorption

Inhibit absorption	Enhance absorption
Calcium-rich foods	Ascorbic acid
Tannins in tea and coffee	Heme iron; ferrous iron (Fe^{2+})
Phytates in cereals	Legumes (remove phytates)

Table 6-3 Iron content of selected foods

Food	Milligrams per serving	Percentage DV*
Iron-fortified cereals, 1 serving	18	(100)
White beans, canned, 1 cup (125mL)	8	(44)
Dark chocolate, 45%-69% cacao solids, 3 ounces (85 g)	7	(39)
Oysters, 6 medium	6	(33)
Beef liver, pan fried, 3 ounces (85 g)	5	(28)
Blackstrap molasses, 1 tablespoon	3.5	(19)
Lentils, boiled and drained, ½ cup (125 mL)	3	(17)
Spinach, boiled and drained, ½ cup (125 mL)	3	(17)
Firm tofu, ½ cup (125 mL)	3	(17)
Kidney beans, canned, ½ cup (125 mL)	2	(11)
Chickpeas, boiled and drained, ½ cup (125 mL)	2	(11)
Tomatoes, stewed and canned, ½ cup (125 mL)	2	(11)
Beef, 3 ounces cooked (85 g)	2	(11)
Baked potato, medium sized	2	(11)
Cashew nuts, oil roasted, 1 ounce (28 g)	2	(11)
Chicken, dark meat, 3 ounces cooked (85 g)	1	(6)

*DV is daily value recommended by the US Food and Drug Administration (USDA). The DV for iron is 18 mg for adults 19 to 50 years old, 27 mg for pregnant women, and 8 mg for adults ≥51 years old. Because iron from plants (nonheme iron) is less efficiently absorbed than that from animal sources (heme iron), the recommended DV for iron in a strict vegetarian diet is approximately 1.8 times higher than that for a nonvegetarian diet. Foods providing 20% or more of the DV are considered to be high sources of a nutrient. For more information on the iron content of specific foods, search the USDA food composition database: http://www.nal.usda.gov/fnic/foodcomp/search/.

Etiologies of iron deficiency anemia

IDA occurs when iron supply is insufficient to meet the iron requirement of developing RBCs. This occurs secondary to blood loss, increased iron requirements, or inadequate iron supply (Table 6-4). A diagnosis of IDA or

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Table 6-4 Causes of iron deficiency

Blood loss
Menstruation, especially abnormal uterine bleeding or heavy menstrual bleeding
Gastrointestinal disorders (esophageal varices, hemorrhoids, peptic ulcer disease, malignancy)
Hookworm or other parasitic infections
Rare causes: pulmonary (hemoptysis, pulmonary hemosiderosis), urologic, or nasal disorders
Repeated blood donations without iron replacement, clinical blood draws, or factitious blood removal
Dialysis, other intravascular hemolysis with hemoglobinuria (eg, paroxysmal nocturnal hemoglobinuria, prosthetic heart valve)
Increased iron requirements
Rapid growth during infancy, young childhood, and adolescence
Therapy with erythropoiesis-stimulating agents
Pregnancy and lactation
Inadequate iron supply
Low iron dietary intake (common in infants and young children; less common as independent cause in adults); vegetarian or vegan diet
Malabsorption, duodenum and upper jejunum diseases (celiac disease, gastric bypass surgery, inflammatory bowel disease)
Achlorhydria, autoimmune atrophic gastritis/*Helicobacter pylori* colonization
Congenital disorders of iron transport (iron-refractory iron deficiency anemia, hereditary hypotransferrinemia, divalent metal transporter 1 disease)

iron deficiency alone (without anemia) requires prompt investigation to determine the underlying cause as it may represent the initial presentation of a number of serious diseases.

In young children, IDA is most commonly due to insufficient dietary iron. Those at particular risk are infants primarily breastfed without sufficient iron supplementation beyond 6 months of age and children with excessive cow milk intake (24 ounces per day or greater). Several factors may act synergistically to cause IDA: (i) low iron content in both breast milk and cow milk, (ii) inhibition of nonheme iron absorption by calcium and milk proteins, (iii) potential for occult intestinal blood loss with cow milk protein enteropathy, and (iv) less consumption of other iron-rich foods by those children with excessive milk intake. In adolescent and adult premenopausal women, menstrual blood loss is the most common cause of iron deficiency. Women are at increased risk for IDA during pregnancy, and this is discussed further under "Anemia associated with pregnancy."

In low and lower-middle income countries, hookworm infection resulting in chronic intestinal blood loss is a common cause of iron deficiency. In higher-income countries, nonparasitic gastrointestinal (GI) blood loss is the most common cause of iron deficiency in adult males and postmenopausal females. Among those with IDA, evaluation of the GI tract employing endoscopic and radiographic methods identifies a causative lesion in ~60% of cases.

Several additional common GI etiologies of iron deficiency are worth noting. Approximately 5% of patients with IDA referred for hematology evaluation have subclinical celiac disease, and this number appears to be higher in those patients who are unresponsive to oral iron therapy. In patients with celiac disease, abnormal iron absorption secondary to villous atrophy of the intestinal mucosa and presence of concomitant inflammation likely both contribute to the anemia. It is unclear whether intestinal blood loss also contributes. Although folate and cobalamin deficiency are known complications of celiac disease, IDA is the most common associated nutritional deficiency.

Accumulating evidence supports a significant role of *Helicobacter pylori* infection in the pathogenesis of IDA. A number of proposed mechanisms include occult GI bleeding, competition for dietary iron by the bacteria, and impaired absorption due to the effect of *H. pylori* on digestive fluid composition. Eradication of *H. pylori* colonization, which can coexist and may share a common pathophysiologic mechanism with autoimmune atrophic gastritis in infected individuals with refractory IDA, has been shown to result in an appropriate response to oral iron therapy and normalization of hemoglobin levels. Autoimmune atrophic gastritis (defined as hypergastrinemia and strongly positive antiparietal cell antibodies) is another common cause of IDA.

Iron-refractory iron deficiency anemia is an extremely rare hereditary disease caused by mutations in TMPRSS6, a transmembrane serine protease, and characterized by a congenital hypochromic, microcytic anemia, and low serum transferrin saturation. TMPRSS6 mutations result in inappropriately elevated hepcidin levels, resulting in patients being refractory to oral iron and only partially responsive to parenteral iron. Although a congenital disease, we mention it here because genetic variants in *TMPRSS6* can determine hemoglobin levels, MCV measurements, and iron status and may modify response to oral iron therapy in iron-deficient patients.

Stages of iron deficiency and clinical manifestations

The manifestations of iron deficiency occur in several stages (Table 6-5), which are defined by the degree of iron depletion. Initially, iron stores in the bone marrow, liver, and spleen are depleted, which is reflected in decreased serum ferritin. As iron stores become exhausted,

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Table 6-5 Laboratory findings in progression from normal iron status to iron deficiency anemia

	Normal	Iron depletion	Iron-restricted erythropoiesis	Iron deficiency anemia
Hemoglobin (g/dL)	Normal	Normal	Normal	Decreased
MCV (fL)	Normal	Normal	Slight microcytosis	Microcytic
Serum ferritin (μg/L)*	~40-200	~20	~10	<10
Iron (μg/dL)	~60-150	~<40	~<20	~<10
TIBC (μg/dL)	Normal	Normal	Normal to mildly increased	Increased
Transferrin saturation (%)	20-50	30	<15	<15
Erythrocyte ZnPP (ng/mL)	~30-70	~30-70	~100	~100-200
Marrow sideroblasts	Present	Present	Absent	Absent

*These values represent pure iron deficiency uncomplicated by inflammatory diseases.

TIBC begins to rise and serum transferrin saturation falls. As erythropoiesis becomes iron restricted, cells become microcytic. Anemia is the final manifestation of iron deficiency.

Iron-deficient individuals may be asymptomatic or have nonspecific symptoms of anemia such as fatigue. Symptoms such as restless legs syndrome, pagophagia (craving for ice), and other forms of pica (cravings for nonfood substances) are more specific for iron deficiency and often improve with initiation of iron therapy. Findings on physical examination may become more pronounced as the iron deficiency worsens and include pallor, stomatitis, glossitis, koilonychia of the nails, and other signs resulting from the effects of iron deficiency on rapidly dividing cells, including the development of red cell hypoplasia. Plummer-Vinson syndrome describes the clinical triad of dysphagia (due to esophageal webs), glossitis, and IDA. Several studies have examined the relationship between iron deficiency and hair loss, primarily in women, with a focus on nonscarring hair loss. However, data have been inconsistent in demonstrating a definitive association.

Diagnosis and treatment

In classic IDA, a patient presents with a clinical history consistent with or concerning for blood loss along with a complete blood count (CBC) demonstrating a microcytic and hypochromic anemia. An elevated platelet count may also be present. Iron studies reveal a low serum ferritin, serum iron, and transferrin saturation and elevated transferrin (or TIBC). The peripheral blood film confirms the microcytosis and hypochromasia and may show increased anisopoikilocytosis (reflected in an increased red blood cell distribution width [RDW]) and bizarrely shaped erythrocytes, including characteristic cigar-shaped or pencil-shaped cells (Figure 6-2). Target cells may be seen and reflect the high area-to-volume ratio of iron-deficient red cells. Table 6-6 compares laboratory assessments found in IDA and anemia of chronic inflammation.

Unfortunately, IDA rarely presents classically, and routine iron studies have limitations that complicate the diagnostic algorithm. Serum ferritin is a stable glycoprotein that accurately reflects bone marrow iron stores in the absence of inflammation. In healthy individuals, serum ferritin is directly proportional to iron stores: 1 μg/L serum ferritin corresponds to approximately 8 to 10 mg of tissue iron stores and is an excellent outpatient screen for iron deficiency. In women of reproductive age, a serum ferritin of <15 μg/L is diagnostic of iron deficiency (defined as no stainable bone marrow iron stores) with a reported specificity and sensitivity of approximately 98% and 75%, respectively. A higher

Figure 6-2 Iron deficiency anemia. There are a variety of red blood cell sizes and shapes. Included among these are hypochromic erythrocytes, microcytes, ovalocytes, and "pencil" cells. Reproduced from ASH Image Bank/Peter Maslak.

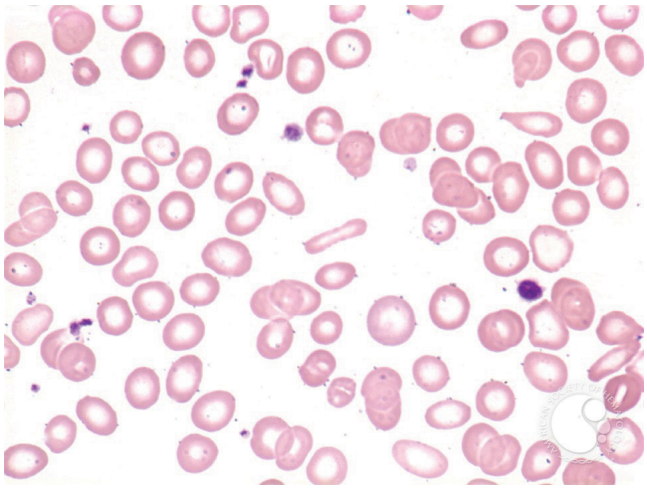

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Table 6-6 Iron studies in iron deficiency anemia versus anemia of chronic inflammation

	Iron deficiency anemia	Anemia of chronic inflammation
Serum ferritin (μg/L)	Decreased	Normal or increased
Iron (μg/dL)	Normal or decreased	Normal or decreased
TIBC; transferrin (μg/dL)	Increased	Normal or decreased
Transferrin saturation (%)	Decreased (<10% to 15%)	Normal or decreased
MCV (fl)	Decreased	Normal or decreased
RDW	Increased	Normal
sTfR/$\log_{10}$ ferritin ratio	>2	<1
Hepcidin	Suppressed	Increased

serum ferritin cutoff for assessing iron deficiency may be appropriate in some populations. In an anemic patient without inflammation, a serum ferritin of <30 μg/L is 92% sensitive and 98% specific in diagnosing IDA. Ferritin is an acute phase reactant, and its plasma level is increased in liver disease, infection, inflammation, and malignancy. Therefore, in patients with chronic inflammatory conditions, evaluation for iron deficiency should include both serum ferritin and transferrin saturation, and a serum ferritin <100 μg/L with transferrin saturation <20% are consistent with iron deficiency. Despite its limitations, low serum ferritin is always consistent with iron deficiency. A serum ferritin level of <30 μg/L is useful in diagnosing iron deficiency in pregnant women (sensitivity of ~90% and specificity of ~85%), who often have an elevated serum transferrin in the absence of iron deficiency.

Serum iron and TIBC are unreliable indicators of iron availability to the tissues because of wide fluctuations in levels resulting from recent ingestion of dietary or medicinal iron, diurnal rhythm, and other factors. If obtained, fasting levels are the most accurate. Transferrin is affected by nutritional status, and transferrin saturation is a calculated measure of serum iron and transferrin.

A number of additional studies can support a diagnosis of IDA when serum ferritin is equivocal. Increased RDW is sensitive for diagnosing IDA but lacks specificity. A trend of decreasing MCV and increasing RDW over time can be instructive. Erythrocyte zinc protoporphyrin (ZnPP) levels are increased in iron deficiency as a result of zinc, rather than iron, being incorporated into the protoporphyrin ring when iron is unavailable. ZnPP has a high sensitivity for detecting iron deficiency but is also increased in lead poisoning, anemia of chronic inflammation, and some hemoglobinopathies. The reticulocyte hemoglobin content or equivalent (CHr or Ret-He) is decreased in IDA and is the first peripheral blood marker of iron-deficient erythropoiesis. This test is limited, however, as patients with thalassemia trait also have decreased values, and may not be widely available. Serum or soluble transferrin receptor (sTfR1) is a circulating protein derived from cleavage of the membrane transferrin receptor on erythroid precursor cells within the marrow. Its level is directly proportional to a person's erythropoietic rate and inversely proportional to tissue iron availability. Iron-deficient patients generally have increased sTfR levels. The incorporation of sTfR1 into the sTfR1-ferritin index (sTfR/$\log_{10}$ ferritin) increases the ability to distinguish IDA from anemia of chronic inflammation than sTfR1 alone. In patients with iron deficiency, the sTfR-ferritin index is elevated (>2) due to increased erythropoietic drive and low iron stores. In contrast, patients with anemia of chronic disease (AOCD) without concomitant iron deficiency are likely to have an sTfR-ferritin index <1. sTfR is also not helpful for identifying iron deficiency in patients with concomitant hemolytic anemias as it remains elevated as a reflection of the patient's underlying hemolysis, independent of iron status.

Serum hepcidin, the primary regulator of iron homeostasis, is suppressed in iron deficiency and elevated in persons with anemia of inflammation. The utility of measuring serum hepcidin in the workup of iron deficiency and other disorders of iron homeostasis has not fully been explored, though differentiation between classic IDA and combined IDA and anemia of inflammation is one potential benefit. Assessment of serum hepcidin may also be beneficial in assessing responsiveness to oral iron therapy in patients with evidence of both iron deficiency and inflammation. While a clinically validated assay became available in 2017, further investigation of its usefulness in widespread clinical practice is warranted.

Evaluation of the bone marrow for stainable iron was previously considered the gold standard for the diagnosis of iron deficiency. High interobserver variability, expense, and invasiveness of the test limit its clinical utility. This procedure is only indicated in atypical patients in whom there is concern for an underlying malignant or infiltrative process.

Once iron deficiency or IDA is confirmed, evaluation for the underlying etiology (Table 6-4) should be initiated. The diagnostic workup should focus on the likely pathologies based on the clinical history for each specific patient. In premenopausal women, menstrual history including abnormal uterine bleeding or heavy menstrual bleeding should be thoroughly assessed. If menstrual blood loss is

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significant and appears to be the primary source of IDA, a trial of iron therapy with close follow-up is reasonable before proceeding to GI studies.

In all male and postmenopausal female patients with confirmed IDA in whom GI blood loss is the most common etiology, upper and lower GI endoscopies should be pursued. Capsule endoscopy to evaluate the small bowel, repeat endoscopic exams, or other diagnostic modalities at the discretion of a gastroenterologist may be required to diagnose obscure GI bleeding (persistent or recurrent bleeding from the GI tract after negative esophagogastroduodenoscopy and colonoscopy). If such evaluations are negative for occult GI blood loss requiring intervention, close follow-up with iron replacement may be a rational approach in some patients.

The definition of *refractory IDA* is not standardized but could be considered in a patient who fails to achieve a 1-g/dL increase in hemoglobin after 4 weeks of therapeutic iron therapy. For patients in whom IDA remains unexplained or refractory despite standard diagnostic workup, some experts advocate serological or biochemical screening for celiac disease with antiendomysial or antitransglutaminase IgA antibodies and atrophic gastritis with gastrin and antiparietal cell antibody testing. Cases of suspected celiac disease should be confirmed by duodenal biopsy. *H. pylori* can be assessed with IgG antibodies or fecal antigen, followed by confirmatory testing with a urea breath test. In patients with iron-refractory or IDA of unknown origin with confirmed *H. pylori* infection, eradication of the infection with standard therapy is reported to be curative and thus should be considered.

An iron absorption test may be useful in evaluating some patients. This simple and minimally invasive test distinguishes an intestinal iron absorption defect from other causes of iron deficiency. Ideally, a patient fasts for ~8 hours, and serum iron is measured at baseline and at 90 minutes after administration of ferrous sulfate (65 to 100 mg elemental iron). In a patient with IDA and normal intestinal iron absorption, the serum iron level is expected to increase by at least 100 μg/dL (minimum of 50 μg/dL) 90 minutes after the oral iron challenge. The test, however, can be difficult to interpret, particularly in nonfasting patients.

The treatment of IDA includes addressing the underlying cause of iron deficiency and replacing the iron deficit. Upfront, it is useful to calculate the patient's approximate iron deficit quantitatively. This includes the amount of iron required to normalize the hemoglobin plus the amount of iron required to replete iron stores [the Ganzoni equation: total iron deficit = weight {kg} × (target Hb − actual Hb) {g/L} × 2.4 + iron stores {mg}]. This quantity should be evaluated in the context of intestinal iron absorption when considering the likelihood of replacing the deficit by oral administration or to define the amount of parenteral iron to administer.

Oral iron supplementation is the preferred initial replacement route in most uncomplicated cases of iron deficiency. Iron salts are the most commonly prescribed treatment for iron deficiency. Ferrous sulfate is available in 325 mg (65 mg elemental iron) tablets, and ferrous gluconate is available in 320 mg (32 mg elemental iron) tablets. Ferrous sulfate elixir (a liquid formulation) is available for infants and young children. In addition to salts, formulations of iron polysaccharide complex and carbonyl iron are available and may be better tolerated. However, most data demonstrate superiority of iron salts due to enhanced absorption compared to these alternative forms. Historically, typical replacement doses of elemental iron in adults ranged from 100 to 200 mg/day and 3 to 6 mg/kg/day in infants and children administered from 1 to 3 times daily. However, recent research has demonstrated in both adults and children that lower doses may be better tolerated, allow for improved adherence, and result in higher fractional iron absorption compared to multiple daily doses. A study of iron-deficient, nonanemic healthy women found that cumulative iron absorption was greater in those receiving alternate-day dosing of oral iron than in those receiving daily dosing. Similar studies are needed for iron-deficient patients with anemia to determine whether the same holds true for that population. However, 65 mg of elemental iron per day in adults and 3 mg of elemental iron per kilogram per day in children, administered once daily, are likely sufficient in the majority of IDA patients.

Nausea, vomiting, epigastric discomfort, and constipation are common dose-dependent side effects of iron salts; approximately 25% of patients cannot tolerate oral iron because of side effects. Patients should be alerted that iron darkens stools. Oral iron salts are absorbed best on an empty stomach but may be better tolerated when taken with foods. Some evidence suggests that even lower doses of oral iron (ie, a single daily dose of 25 mg of elemental iron) remain effective and result in lower rates of adverse effects, though it is unknown whether such a low dose regimen requires longer duration of therapy. Antacids, the tannins found in tea, calcium supplementation, bran, and whole grains can all decrease iron absorption if taken concurrently with oral iron. Treatment with oral iron to replenish iron stores should continue for approximately 3 months after the hemoglobin normalizes. Assessment of serum ferritin prior to discontinuation of iron therapy may be performed to ensure that iron stores have been sufficiently replenished.

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Oral heme iron polypeptide, derived through the proteolytic digestion of porcine hemoglobin, is another available oral iron formulation. Heme iron (derived from hemoglobin and myoglobin in animal food sources) is more efficiently absorbed and via a different, undefined mechanism, than nonheme iron. Limited data compare oral heme iron polypeptide to other oral iron formulations; therefore, its true efficacy is unknown. It is currently more expensive than oral iron salts.

Parenteral iron is indicated when there is nonadherence with or intolerance to oral iron therapy, high iron requirements, or concern for intestinal malabsorption or concomitant inflammation. Intravenous iron therapy is also recommended by the American Heart Association for adults with heart failure and concomitant iron deficiency.

Six parenteral iron preparations are now available in the United States (iron sucrose, ferric gluoncate, low-molecular-weight iron dextran, ferumoxytol, ferric carboxymaltose, and ferric derisomaltose). Iron sucrose and ferric gluconate both have very low incidence of anaphylaxis, and their administration does not require a test dose. Side effects of iron sucrose and ferric gluconate include mild arthralgia and myalgia. The principal disadvantage is the inability to give a total replacement dose in a single infusion, with a typical limitation of 200 to 300 mg per infusion. GI and vasoactive reactions occur at doses greater than 200 to 400 mg. Low-molecular-weight iron dextran is considerably safer than its previous high-molecular-weight counterpart but carries a black box warning and requires a test dose prior to full dose infusion. The advantages of low-molecular-weight iron dextran include its low cost and the ability to give replacement doses of iron in a single or "total-dose" infusion. Ferumoxytol, ferric carboxymaltose, and ferric derisomaltose also allow for larger doses to be administered per infusion. Ferumoxytol also carries a black box warning due to low but serious risk of severe and potentially fatal allergic reactions. Ferric carboxymaltose is associated with hypophosphatemia.

IDA patients receiving iron replacement therapy demonstrate reticulocytosis within 7 to 10 days of initiating treatment. Hemoglobin response generally occurs within 2 weeks but may take longer to fully correct, and serum ferritin corrects once additional iron (beyond that to correct the hemoglobin) accumulates to replenish body stores, as long as the underlying etiology has been appropriately identified and fully corrected. Failure to respond to oral iron should prompt consideration of patient nonadherence, inadequate replacement dosing, poor iron absorption, ongoing blood loss, or appropriateness of the diagnosis.

KEY POINTS

- Iron deficiency is the most common cause of anemia worldwide, and its diagnosis requires an evaluation for the underlying etiology.
- Young children most commonly have nutritional IDA due to insufficient dietary iron, while adolescent and adult premenopausal women are at risk for IDA due to chronic menstrual blood loss.
- In adult men and postmenopausal women, GI blood loss is the most common cause of IDA.
- IDA is the most common nutritional deficiency associated with celiac disease.
- Classic iron deficiency is characterized by a hypochromic, microcytic anemia, elevated RDW, and low corrected reticulocyte count.
- A ferritin of <15 µg/L in any individual is diagnostic of iron deficiency. Higher thresholds may be more appropriate for some populations.
- Oral iron supplementation is the preferred replacement route in most uncomplicated cases of iron deficiency. Intravenous replacement may be utilized in patients with refractory IDA, intolerance of oral iron therapy, excessive blood loss, inflammation, or malabsorption.
- Failure to respond to oral iron should prompt consideration of ongoing blood loss, inadequate replacement dosing, or poor absorption due to underlying GI pathology (eg, celiac disease, *H. pylori* infection, or atrophic gastritis).

Normocytic anemias

Anemia of inflammation (anemia of chronic disease)

CLINICAL CASE

A 44-year-old woman is referred for evaluation of a hypoproliferative normocytic anemia with a hemoglobin of 8 g/dL. Her past medical history is significant for a mitral valve replacement 1 year earlier. Recently, she has developed low-grade fevers, malaise, and generalized fatigue. Her examination is remarkable for a temperature of 38.5°C and a 2/6 systolic ejection murmur over the mitral valve. Laboratory evaluation reveals that serum ferritin is 95 ng/mL, transferrin saturation is 12%, and an elevated erythrocyte sedimentation rate (ESR) at 92 mm/h. Blood cultures subsequently return positive for α-hemolytic streptococci. Transesophageal echocardiogram confirms subacute bacterial endocarditis of the prosthetic mitral valve. The patient is treated with penicillin and gentamicin. Four weeks later, the hemoglobin increases to 11 g/dL.

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Overview

Anemia is common in patients with chronic inflammatory conditions such as malignancy, autoimmune disease, chronic infection, and chronic kidney disease. The resulting anemia is termed the *anemia of inflammation* or the *anemia of chronic disease*. It is now recognized that patients with conditions not traditionally thought to be inflammatory, such as trauma, postsurgical, and periods of prolonged critical illness, may also develop AOCD. AOCD is reflective of underlying disease activity, and evaluation for an underlying disorder is warranted when considering AOCD as the cause of anemia. Patients with AOCD typically have hemoglobin levels in the range of 7 to 11 g/dL. AOCD is characterized as a normochromic, normocytic anemia with a low corrected reticulocyte count in a patient with a clinical history of chronic disease or condition with underlying inflammation. Over time, however, the anemia resulting from prolonged iron-restricted erythropoiesis may become more severe and with microcytic and hypochromic indices. Iron studies are often obtained with the goal of distinguishing AOCD from IDA. In AOCD, serum iron and iron-binding capacity are typically low to normal, and ferritin is normal or elevated (Table 6-6). In many but not all conditions, an elevated ESR or C-reactive protein supports the diagnosis of AOCD.

Multiple processes are involved in the pathogenesis of AOCD. Cytokines, such as tumor necrosis factor alpha, interleukin 1, interleukin 6, and interferons, play a central role. These cytokines cause a reduction in the proliferation of erythroid precursors in response to EPO, a decrease in the EPO production relative to the degree of anemia, and a moderate decrease in RBC survival. The hallmark of AOCD is an alteration in iron metabolism. Inflammatory cytokines, especially IL-6, increase hepatic synthesis of hepcidin, the key regulator of cellular iron homeostasis. As previously mentioned, hepcidin acts by binding the iron export protein, ferroportin, leading to its degradation and thereby inhibiting intestinal iron absorption and macrophage iron recycling. This results in iron-restricted erythropoiesis, which is reflected in less available circulating iron (ie, low plasma iron and transferrin saturation levels).

In infants and young children, anemia due to inflammation does not require the presence of an underlying chronic inflammatory disorder. Minor acute bacterial or viral infections, when recurrent, can cause a mild normocytic anemia with blunted reticulocyte response within a few weeks. This form of anemia of inflammation is self-limited and resolves when the infant or child's infection resolves.

In most patients, AOCD is mild and improves with treatment of the underlying disorder. However, some patients may have concomitant iron deficiency or functional iron deficiency. Assessment of a serum or sTfR and/or the sTfR-ferritin index may assist in determining whether iron deficiency is also present in a patient with AOCD. The elevation of hepcidin results in decreased absorption of iron from the diet and oral supplements. Thus, in patients with concomitant iron deficiency and AOCD, treatment with intravenous iron therapy, particularly in patients in whom the underlying inflammation cannot be controlled, may be beneficial. Future treatment options for AOCD may involve decreasing hepcidin.

KEY POINTS

- AOCD is the most common cause of anemia in patients with underlying inflammatory diseases.
- AOCD is characterized by a normocytic or microcytic anemia and low corrected reticulocyte count. Iron studies typically demonstrate decreased serum iron, normal or decreased transferrin (or TIBC), and decreased transferrin saturation, along with a normal or increased serum ferritin.
- The pathophysiology of AOCD is multifactorial, but the sequestration of iron secondary to elevation in serum hepcidin plays a central role.
- Primary treatment should be directed at the underlying medical condition.

Anemia associated with chronic kidney disease

CLINICAL CASE

A 71-year-old woman presents to her primary care physician with increasing dyspnea on exertion. She is found to have a hypoproliferative, normocytic anemia (hemoglobin, 9.5 g/dL), and a creatinine level of 2.2 mg/dL. Iron studies were normal. She was started on an erythropoiesis-stimulating agent (ESA) along with an oral iron supplement. Within 4 weeks, she had good clinical response; however, 2 months later, she returns with recurrent exertional dyspnea. Laboratory values reveal a hemoglobin of 9.7 g/dL and an MCV of 77 fL. Iron studies are consistent with IDA. Intravenous iron therapy is administered with good clinical response.

Overview

Anemia of chronic kidney disease is primarily due to underproduction of EPO due to a decrease in the

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number of renal cortical cells available to produce the hormone and accumulation of uremic toxins. Impaired RBC deformability and membrane permeability secondary to uremia, secondary hyperparathyroidism, RBC fragmentation from hemodialysis, or increased blood loss, and exposure to RBC toxins may also contribute. Excessive hepcidin in CKD patients, resulting in iron-restricted erythropoiesis related to AOCD, contributes as well and may be due in part to its reduced renal clearance and/or increased inflammatory-mediated expression; levels in CKD are further influenced by iron and ESA administration. As in other patients with AOCD, elevation in serum hepcidin impairs both dietary iron absorption and iron release from body stores and may account for ESA resistance observed in some patients. Increased iron demand and utilization related to ESA therapy also contributes to anemia of CKD.

Anemia of CKD is typically normochromic and normocytic with a low reticulocyte count, unless complicated by iron deficiency or other vitamin deficiencies. Peripheral film is often normal, but, in rare patients with severe kidney failure, echinocytes can be seen (characterized by irregular broad-based short blunt projections of the RBC membrane).

The bone marrow is normocellular, but a hypocellular marrow with relative erythroid hypoplasia and marrow fibrosis (osteitis fibrosa) related to secondary hyperparathyroidism has been described. Iron studies may be normal or may show low serum iron levels accompanied by low serum transferrin and elevated serum ferritin, consistent with AOCD.

It is well established that recombinant human EPO and other ESAs improve the anemia associated with CKD. However, use of ESAs in CKD patients to target normal or near-normal hemoglobin values is associated with increased risk of adverse cardiovascular events and mortality. Conversely, only modest to minimal improvement in patient-reported outcomes such as fatigue have been demonstrated with ESAs' targeting of lower target hemoglobin levels. Randomized control studies are needed to define both the optimal hemoglobin concentration for initiation of ESA therapy and a therapeutic target to achieve improved clinical and patient-reported outcomes, as well as the best use of intravenous iron to reduce total ESA dosing requirements. A novel class of agents, prolyl hydroxylase inhibitors, are available to treat the anemia of CKD. These drugs stabilize the hypoxia-inducible factor complex and stimulate endogenous EPO production, even in those patients with end-stage kidney disease. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative and Kidney Disease: Improving Global Outcomes provide nephrologists with guidelines on the management of anemia associated with CKD based on available evidence and expert opinion.

KEY POINTS

- Anemia associated with CKD is primarily due to an EPO deficiency. However, multiple pathophysiologies likely contribute, including AOCD.
- ESAs are effective treatment of anemia associated with CKD.
- ESAs and IV iron treatment of anemia associated with CKD require careful consideration of the potential benefits and harms to the individual patient.

Macrocytic anemias

Megaloblastic anemias

Megaloblastic anemias result from impaired DNA synthesis in hematopoietic cells and are characterized by macrocytosis with marked variation in the size and shape of red blood cells (often macro-ovalocytes), a low corrected reticulocyte count, hypersegmented neutrophils, and occasionally pancytopenia. Megaloblastic changes in the marrow result from the dyssynchrony between nuclear and cytoplasmic maturation and include the following: hypercellular marrow with an erythroid predominance (reversed myeloid:erythroid ratio), presence of giant pronormoblasts, and giant metamyelocytes. An imbalance of iron quantity endocytosed by marrow erythroblasts versus that incorporated into circulating erythrocytes reflects ineffective erythropoiesis and implies cell death within the marrow during erythroid differentiation. Peripherally, these changes are reflected by elevated lactic dehydrogenase, elevated unconjugated bilirubin, and low haptoglobin and the occasional appearance of red cell fragments on peripheral film.

Megaloblastic anemias and MDS share a number of clinical findings, and MDS should be considered in the differential diagnosis during initial evaluation. Hypercellular marrow with giant pronormoblasts, as seen in megaloblastic anemias, may also lead to an incorrect diagnosis of acute leukemia. Cobalamin and folate deficiencies are the most common causes of megaloblastic anemias.

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Vitamin B_{12} deficiency

CLINICAL CASE

A 62-year-old woman with a history of vitiligo presents with progressive onset of fatigue and pallor. On review of systems, she additionally endorses occasional nausea and abdominal bloating with 5-10 pounds of unintentional weight loss. On examination, he is pale, has mild peripheral edema, and minimal loss of position and vibratory senses in the feet bilaterally. Laboratory evaluation reveals a hemoglobin of 7.1 g/dL, MCV of 109 fL, with normal neutrophil and platelet counts. Serum cobalamin level is 72 pg/mL, serum folate is normal, and methylmalonic acid (MMA) and homocysteine (HCY) are both elevated. He is started on daily intramuscular cobalamin replacement, with symptomatic improvement and brisk reticulocytosis noted within 1 week. Subsequent evaluation by a gastroenterologist confirms the presence of both antiparietal cell antibodies and antibodies to intrinsic factor, confirming the diagnosis of pernicious anemia (PA).

Background

Vitamin B_{12} (cobalamin) functions as an essential coenzyme for cytoplasmic methionine synthase and methylmalonyl-CoA mutase. Cytoplasmic methionine synthase catalyzes methylation of homocysteine to methionine, which is linked to folate metabolism, as the methyl group transferred to homocysteine is provided by the conversion of 5-methyl tetrahydrofolate to tetrahydrofolate. Tetrahydrofolate is essential for purine and pyrimidine synthesis. Methylmalonyl-CoA mutase catalyzes the conversion of methylmalonyl-CoA to succinyl-CoA in the mitochondria, and succinyl-CoA then enters the Krebs cycle.

Humans are completely dependent on dietary (predominantly animal) sources of cobalamin. In the stomach, released cobalamin is bound to the protein haptocorrin, present in saliva and gastric fluids, which protects the vitamin from degradation within the acidic stomach environment. In the duodenum, pancreatic enzymes degrade haptocorrin, and cobalamin subsequently binds to intrinsic factor, which is synthesized and secreted by the parietal cells of the stomach. Intrinsic factor-bound cobalamin is endocytosed by the receptor complex cubam in the terminal ilium. Inside the ileal enterocyte, intrinsic factor is degraded, and the released cobalamin exits the basolateral cell surface via a transporter. In the plasma, cobalamin binds to transcobalamin II for delivery to tissues.

Cobalamin deficiency results most commonly from abnormal intestinal absorption or, rarely, from insufficient dietary intake or defects in bodily transport. Select causes of cobalamin deficiency are listed in Table 6-7.

Table 6-7 Select causes of vitamin B_{12} deficiency

Impaired absorption
Deficiency of intrinsic factor or IF-bound vitamin B_{12} uptake; congenital intrinsic factor deficiency
Pernicious anemia or other gastric atrophy (*Helicobacter pylori* or autoimmune gastritis)
Gastric bypass surgery
Decreased ileal absorption of vitamin B_{12} (Imerslund-Gräsbeck syndrome)
Hypochlorhydria (impairs release of B_{12} from dietary proteins)
Age
Medications (proton-pump inhibitors, H_2 antagonists, metformin [mechanism unknown], nitrous oxide abuse)
Inadequate pancreatic protease (vitamin B_{12} remains sequestered by haptocorrin)
Intestinal competition for host vitamin B_{12} (tapeworm *Diphyllobothrium latum*)
Ileal resection, bypass or dysfunction (Crohn disease, celiac disease, intestinal lymphoma, bacterial overgrowth from blind loop syndrome)
Insufficient dietary intake
Strict vegans, some vegetarians, breastfed infants of vitamin B_{12}–deficient mothers
Defects in bodily transport
Congenital disorders of vitamin B_{12} transport (defects in cubam, transcobalamin, others)

IF, intrinsic factor.

Due to efficient enterohepatic circulation and renal reuptake, cobalamin is retained in the body for long periods, and dietary cobalamin deficiency therefore develops slowly over a period of years.

The most common cause of symptomatic cobalamin deficiency is pernicious anemia, PA. PA is an autoimmune disorder in which antibodies to gastric parietal cells cause gastritis and mucosal atrophy of the body and fundus of the stomach. Such atrophy reduces the number of parietal cells that produce intrinsic factor, required for vitamin B_{12} absorption, which, in turn, is required for erythropoiesis and myelin synthesis. PA is frequently associated with other autoimmune disorders (eg, type 1 diabetes, autoimmune thyroiditis, primary hyperparathyroidism, and vitiligo). Diagnosis includes demonstration of a megaloblastic anemia and low serum vitamin B_{12} level accompanied with elevated methylmalonic acid and homocysteine. The sensitivity and specificity of antibodies to intrinsic factor and parietal cell are both low, though, if present, are also supportive of the diagnosis. The gastric enzyme H^+/K^+ ATPase is the target antigen recognized by parietal cell antibodies but may be positive in persons with other autoimmune diseases, as well as healthy

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individuals, and is therefore less helpful. Stomach biopsy or serum biomarkers consistent with chronic atrophic gastritis are not required for the clinical diagnosis of PA.

Some data suggest long-standing *H. pylori* infection in the pathogenesis of PA and atrophic body gastritis. One hypothesis suggests that over time the infection is replaced by an autoimmune process mediated by autoreactive gastric T-cells, which recognize H^+/K^+-ATPase and *H. pylori* antigens. These autoreactive cells cause irreversible mucosal damage. It is unclear whether PA should be included among the long-term consequences of *H. pylori* gastritis, and thus *H. pylori* testing in the evaluation of patients with PA remains controversial.

PA patients are at risk for development of gastric adenocarcinoma and carcinoid tumors. Data are insufficient to support routine subsequent endoscopic surveillance of these patients, however, and follow-up should be individualized to the patient.

Nitrous oxide is associated with an acute megaloblastic anemia secondary to impaired cobalamin metabolism. Abuse of this compound has been associated with psychosis and other neurologic defects.

Diagnosis

Cobalamin deficiency can present insidiously with unexplained anemia, neuropsychiatric symptoms, or GI manifestations, including swollen or sore tongue (glossitis), anorexia, and diarrhea. Neurologic symptoms include paresthesia, unsteady gait or clumsiness, and motor weakness progressing to paralysis. Psychiatric symptoms include mania, paranoia, and irritability. Within the nervous system, cobalamin deficiency leads to defective myelin synthesis resulting in central and peripheral nervous system dysfunction. In the spinal cord, subacute combined degeneration occurs, affecting its posterior and lateral columns, which presents clinically as loss of vibratory sense and proprioception. Magnetic resonance imaging (MRI) shows symmetrical increased T2 signal intensity in the posterior or posterolateral columns, commonly confined to the cervical and thoracic spinal cord. Brain involvement in cobalamin deficiency on MRI has also been reported.

Early recognition of these signs and symptoms is critical to avoid irreversible neurologic dysfunction. While both folate and cobalamin deficiencies result in megaloblastic anemia, only cobalamin deficiency results in neuropsychiatric symptoms. Therefore, cobalamin levels always should be measured before initiation of folate in patients at risk for concomitant cobalamin deficiency. Folate replacement alone may improve hematologic manifestations in patients with cobalamin deficiency, thereby masking the underlying cobalamin deficiency, thereby allowing neurologic deficits to progress. While hematologic changes are typically present early, some patients may present with neurologic involvement in the absence of accompanying anemia. It is unknown why some patients develop one set of symptoms over the other. However, macrocytic anemia cannot be used as the sole criterion for pursuing the diagnosis. Accordingly, any patient with unexplained neuropathy should be assessed for cobalamin deficiency.

Cobalamin deficiency is a rare and treatable cause of failure to thrive and delayed development in infants. Its long-term developmental consequences remain unknown. In developed countries, deficiency can occur in infants exclusively breastfed by mothers who are themselves deficient in cobalamin (eg, unrecognized PA, strict vegetarian or vegan diet), causing low cobalamin body stores in the infant at birth and inadequate amounts of cobalamin in the breast milk. Signs and symptoms often present between the ages of 4 and 12 months and include failure to thrive, lethargy, hypotonia, and arrested or regressed developmental skills. It can rarely cause seizures or brain atrophy on imaging. Infants may demonstrate abnormal movements, including tremor, myoclonus, and choreoathetoid movements.

Rare cases of cobalamin deficiency due to a congenital defect in intrinsic factor secretion from parietal cells (ie, congenital PA) present around 18 to 36 months of age, after the depletion of fetal liver stores. Though much less common than adults, acquired PA may present in children as well, particularly those with other autoimmune conditions. The Imerslund-Gräsbeck syndrome is a rare congenital defect in cobalamin absorption resulting from mutations in the cubam receptor complex. In some cases, this autosomal recessive disorder also causes proteinuria, which is related to cubam's function in the renal reabsorption of some filtered proteins. Transcobalamin II deficiency is inherited as an autosomal recessive trait that presents in early infancy with severe megaloblastic anemia despite the presence of normal intrinsic factor secretion, cobalamin absorption, and cobalamin levels.

No gold standard test exists for diagnosing cobalamin deficiency because each laboratory test has its disadvantages. A serum cobalamin assay, which quantifies all forms of cobalamin in serum, is the standard initial routine diagnostic test. It is a widely available, inexpensive, and automated method based on intrinsic factor binding of cobalamin and immune chemoluminescence. Unfortunately, the assay lacks sensitivity and specificity and demonstrates highly variable results. Both significant intraindividual variation and large absolute differences in results may be seen on repeat testing. In patients in whom cobalamin deficiency is clinically suspected, a serum cobalamin level <200 pg/mL

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supports the diagnosis. It is important to note that, given the significant diagnostic limitations of serum cobalamin measurements, values above this cutoff do not exclude the diagnosis and hematologists need to carefully consider the clinical scenario of each case. For example, spuriously high cobalamin levels have been reported in patients with PA, which has been attributed to assay interference by high levels of antibodies against intrinsic factor. Adequate cobalamin treatment is the safest approach if the clinical presentation and laboratory studies are confusing. Complete resolution of symptoms with therapy supports the diagnosis of cobalamin deficiency. Once cobalamin deficiency is diagnosed, evaluation for the underlying cause is necessary.

Methylmalonic acid and total HCY are more sensitive indicators of early cobalamin deficiency as serum levels of both MMA and HCY become elevated before cobalamin levels fall below the lower limits of the normal range. Elevations in one or both have been shown to correlate with clinical response to therapy. In patients with equivocal serum cobalamin levels and in whom clinical suspicion persists, metabolite testing with MMA and HCY is reasonable. Testing MMA and HCY levels is reasonable in patients with atypical clinical findings in whom cobalamin deficiency is being considered and in asymptomatic patients incidentally found to have a low cobalamin level. HCY levels, but not MMA, are also elevated in patients with folate deficiency. There is debate regarding the clinical importance of laboratory tests suggesting cobalamin deficiency in patients without overt cobalamin deficiency symptoms (ie, absence of neurologic and hematologic findings), so-called subclinical cobalamin deficiency. Many patients with subclinical cobalamin deficiency do not progress to symptomatic cobalamin deficiency. It remains unknown whether these patients have subtle and clinically unrecognized symptoms of cobalamin deficiency. It is debated whether treatment and/or close follow-up is indicated. These discrepancies reflect a lack of uniform diagnostic criteria for subclinical cobalamin deficiency and the limitations in laboratory testing for cobalamin deficiency. Therefore, routine screening of asymptomatic individuals for cobalamin deficiency is not recommended.

Low cobalamin levels alone (without megaloblastic anemia or neurological symptoms) may be seen in association with a variety of conditions, including pregnancy (due to changes in protein binding), folate deficiency, and use of certain drugs (eg, oral contraceptives and metformin). True cobalamin deficiency in these situations can be confirmed by elevations in MMA and HCY levels. Other conditions can cause an elevated level of HCY alone (hypothyroidism, vitamin B_6 deficiency), MMA alone (intestinal overgrowth), or both (renal failure).

Testing for intrinsic factor antibodies alone or with antiparietal cell antibodies may be performed in patients with evidence of low cobalamin; additional testing for nonspecific serum gastrin or pepsinogen levels in individual cobalamin-deficient patients (predicted to be elevated and low in deficient patients, respectively) may be indicated as well. The incidence of intrinsic factor antibodies increases to 60% to 80% with increasing disease duration. As cobalamin therapy can cause false-positive results on intrinsic factor antibody testing, assessment should occur at least a week after a cobalamin injection to ensure accurate results. Parietal cell antibodies are present in 80% to 90% of PA patients, especially in the early stages of the disease. Later in the disease course, the incidence of parietal cell antibodies decreases due to the progression of autoimmune gastritis and loss of gastric parietal cell mass. Parietal cell antibodies lack specificity and can also be found in other autoimmune diseases (ie, Hashimoto thyroiditis or type 1 diabetes) or in older subjects, at low frequency. Historically, the Schilling test was used to measure cobalamin absorption, but this test is no longer available in most centers.

Treatment

The majority of patients with cobalamin deficiency can be treated with oral cobalamin replacement. Parenteral therapy is recommended for patients with significant symptoms (initially) as well as those with PA. For patients with PA, intramuscular cobalamin is given in doses of 1000 μg/day (up to 150 μg is retained from each injection by most patients) for 1 week, then 1000 μg/weekly for 4 weeks, and then 1000 μg/month or less frequently. Alternative dosing regimens can be used. Excess cobalamin is excreted in the urine, so toxicity due to excessive vitamin replacement does not occur. The observation of intrinsic factor–unrelated diffusion of ~1.2% of oral cobalamin (any dose) suggests that oral cobalamin may be a safe and effective treatment in some patients, even with low levels of intrinsic factor. The initial oral replacement dose begins at 1000 to 2000 μg/day. Patients should be observed carefully to ensure that symptoms of anemia improve. After cobalamin replacement is initiated, some patients become iron deficient due to more efficient iron uptake by developing erythroid cells, which then requires iron replacement as well. Additionally, hypokalemia may develop during the initial week of therapy, particularly in severely deficient patients, due to the uptake of potassium during erythropoiesis.

Following cobalamin replacement, the bone marrow shows resolution of megaloblastic changes within hours. Reticulocytes appear in the peripheral blood, typically

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peaking approximately 1 week after initiating replacement therapy. Neutrophil hypersegmentation may persist for up to 2 weeks. Blood counts and MCV return to normal in 2 to 3 months. Neurologic abnormalities usually improve within 3 months; though in some patients, this may take up to 12 months. In some individuals, the neurological deficits are irreversible.

KEY POINTS

- The most common etiology of cobalamin deficiency is impaired absorption, typically due to autoimmune gastritis (ie, pernicious anemia), which results in symptomatic deficiency.
- Both cobalamin and folate deficiencies cause a megaloblastic anemia; however, neuropsychiatric symptoms are seen only in cobalamin (vitamin B_{12}) deficiency.
- The diagnosis of cobalamin deficiency can be made by a low serum cobalamin level, along with elevated MMA and HCY levels.
- Oral cobalamin replacement may be utilized in many patients, though patients with PA often require intramuscular cobalamin replacement long-term. Parenteral cobalamin replacement therapy is recommended for patients with any neuropsychiatric symptoms.

Folate deficiency

CLINICAL CASE

A 55-year-old man presents for routine physical examination. He complains of fatigue and shortness of breath. He admits to daily excessive alcohol consumption since he lost his job 6 months ago. Physical examination reveals pallor, glossitis, a flow murmur, and a normal neurological examination. Laboratory evaluation reveals a hemoglobin of 7.1 g/dL, MCV of 130 fL, neutrophil count of 1000/μL, and platelet count of 55,000/μL. A serum folate level is 1 ng/mL; cobalamin level is 350 pg/mL. Methylmalonic acid level is normal; homocysteine is elevated. He is enrolled in an alcohol treatment program and started on 2 mg of daily oral folic acid replacement with symptomatic improvement and brisk reticulocytosis noted within 2 weeks.

Background

Folate exists in nature as a conjugate with glutamic acid residues. Folate, when reduced to tertrahydrofolate, is involved in 1 carbon metabolism. Thus, it is critical for the synthesis of purines and pyrimidines and for amino acid metabolism. Though rare, a loss-of-function mutation in the gene encoding a proton-coupled high-affinity folate transport protein (PCFT/HCP1) within the duodenum and jejunum results in a syndrome of hereditary folate malabsorption.

Folate deficiency is rare and significantly less common than cobalamin deficiency. It may result from impaired absorption (ie, sprue, Crohn disease, or celiac disease) or increased utilization (Table 6-8), but the principal cause is decreased dietary intake. Green leafy vegetables, citrus fruits and juices, dried beans, and peas are all natural sources of folate. The implementation of folic acid fortification in grains has drastically reduced the prevalence of folate deficiencies in many countries. The FDA-recommended daily dietary folate equivalent is 400 μg. Folate deficiency due to inadequate dietary intake can develop within a few months because body stores are not extensive. Infants who are exclusively fed unfortified goat's milk are at risk for the development of folate deficiency. Folate supplementation should be part of routine prenatal care to reduce the risks of neural tube defects in infants and should also be considered in other patients with increased folate requirements (eg, some forms of chronic hemolysis with high red cell turnover, such as pyruvate kinase deficiency, and some sickle cell disease patients). Folate deficiency is common in persons with alcohol use disorders and results from a combination of reduce intake, malabsorption, and increased urinary excretion.

Table 6-8 Select causes of folate deficiency

Insufficient dietary intake
Poor intake of fruits and vegetables or prolonged cooking of these foods
Alcoholism (alcohol increases renal folate excretion and impairs intracellular metabolism)
Impaired absorption
Intestinal dysfunction (Crohn disease, celiac disease)
Congenital abnormality in intestinal folate transporter (mutations in *PCFT*)
Increased requirements
Increased cellular proliferation
Pregnancy and lactation
Hemolytic anemia (sickle cell anemia, warm autoimmune hemolytic anemia)
Malignancies (associated with a high proliferative rate)
Exfoliative dermatitis
Hemodialysis
Medication affecting folate metabolism or absorption (methotrexate, phenytoin, carbamazepine)

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Diagnosis and treatment

The hematologic manifestations of folate deficiency are indistinguishable from cobalamin deficiency. However, folate deficiency does not cause the neuropsychiatric manifestations such as subacute combined degeneration that occurs with cobalamin deficiency. Folate deficiency is strongly implicated in increasing the incidence of fetal neural tube defects. Plasma (or serum) folate undergoes diurnal changes related to recent food intake, which limits the usefulness of the diagnostic assay. If the serum folate is >4 ng/mL, folate deficiency is unlikely. A serum folate concentration of <2 ng/mL is more consistent with folate deficiency. Alternatively, RBC folate levels have less daily variability and more accurately reflect the average folate content of the circulating RBC population. However, RBC folate levels may also be low in persons with cobalamin deficiency. Folate deficiency results in high levels of HCY but not MMA. Assessment for cobalamin deficiency should always be performed prior to initiation of folate therapy because folic acid can partially reverse the hematologic abnormalities of cobalamin deficiency, while the neurologic symptoms resulting from cobalamin deficiency progress. Treatment with folic acid (1 to 5 mg per day) should be prescribed for 1 to 4 months or until complete hematologic recovery occurs. Folate is inexpensive and effective even in persons with malabsorption.

KEY POINTS

- The most common cause of folate deficiency is decreased dietary intake.
- Folate supplementation should be part of routine prenatal care.
- Patients with some forms of chronic hemolytic anemia (eg, pyruvate kinase deficiency) should receive daily folate supplementation.
- HCY is elevated, and MMA is normal in folate deficiency.
- Cobalamin deficiency should be ruled out prior to initiating treatment with folate.

Other causes of megaloblastic anemia

In addition to folate and cobalamin deficiency, there are other rarer causes of megaloblastic anemia. Drugs that affect DNA synthesis are the most likely cause of megaloblastic anemia in the absence of folate and cobalamin deficiency. The most common drugs include 5-fluorouracil (pyrimidine analog), azathioprine (purine analog), and methotrexate (antifolate). Hydroxyurea, zidovudine, and several antiepileptic drugs (AEDs) also likely inhibit DNA synthesis. Drug-induced macrocytosis is typically less significant (MCV <110) compared to the megaloblastic changes seen in patients with cobalamin and folate deficiencies.

Acquired pure red cell aplasia

CLINICAL CASE

A 64-year-old woman presents with fatigue and dyspnea on exertion, which has been progressive over the last 2 months. She is not taking any medications and has no significant past medical history. Previous blood counts reportedly have been normal. Physical examination is significant for skin pallor and pale conjunctivae. Laboratory evaluation reveals hemoglobin of 6.4 g/dL, MCV of 99 fL, absolute reticulocyte count of <10,000/μL, and corrected reticulocyte count of 0.3%. White blood cell and platelet counts are normal. Bone marrow examination reveals a maturation arrest at the proerythroblast stage. Flow cytometry does not reveal a lymphoproliferative disorder, and cytogenetic evaluation results are normal. Computed tomography (CT) scan of the chest fails to identify a thymoma. Prednisone 1 mg/kg daily is prescribed, and within 2 weeks, a partial response is seen. After 6 weeks, a complete response is seen, and a slow taper of prednisone is begun. The patient relapses after prednisone withdrawal. She is begun on cyclosporine with a gradual but complete response in her blood counts.

Background

Pure red cell aplasia is characterized by a severe normochromic, normocytic or macrocytic anemia with reticulocytopenia and either an absence of hemoglobin-containing cells (<3% of the nucleated marrow cells) or maturation arrest at the proerythroblast stage (Figure 6-3). If PRCA is secondary to large granular lymphocyte leukemia or another lymphoproliferative disorder, the marrow shows lymphocytic infiltration.

PRCA occurs as either an acquired or congenital (Diamond-Blackfan anemia; see Chapter 15) disorder. Acquired PRCA is further classified as primary or

Figure 6-3 Pure red cell aplasia bone marrow aspirate with excess proerythroblasts. Arrows indicate proerythroblasts. Wright-Giemsa–stained marrow aspirates from a normal patient (a) and a pure red cell aplasia patient (b) are shown.

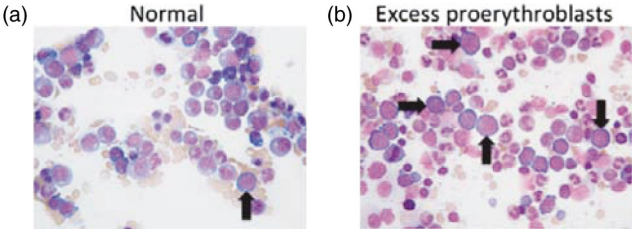

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Table 6-9 Classification of pure red cell aplasia

Congenital pure red cell aplasia
Diamond-Blackfan anemia
Acquired pure red cell aplasia
Primary pure red cell aplasia (likely immune-mediated mechanism)
Transient erythroblastopenia of childhood
Idiopathic
Secondary pure red cell aplasia (immune consequence of an underlying disorder)
Thymoma: post-ABO and autoimmune
Hematologic malignancies (eg, chronic lymphocytic leukemia, large granular lymphocyte leukemia, multiple myeloma)
Solid tumors (eg, stomach, breast, lung, renal cell carcinomas)
Infectious (eg, HIV, EBV, viral hepatitis)
Collagen vascular diseases
Drugs and chemicals (EPO antibodies may develop in those treated with ESAs)
Post-ABO incompatible bone marrow transplantation
Autoimmune chronic hepatitis or hypothyroidism
Parvovirus B19 (virus directly cytotoxic to red blood cell precursors)
Myelodysplastic syndrome (hematopoietic stem cell unable to differentiate along erythroid lineage)

EBV, Epstein-Barr virus

secondary, depending on the absence or presence of an associated disease, infection, or drug (Table 6-9). Alternatively, acquired PRCA can be classified by the pathophysiology of the anemia. Erythropoiesis can fail by 3 distinct mechanisms. In most cases of PRCA, an aberrant immune response leads to suppression of RBC development: erythroid progenitor cells are intrinsically normal but their differentiation is inhibited by a humoral or T-lymphocyte–mediated mechanism. The majority of cases are idiopathic. In about 10% of cases, PRCA results from chronic parvovirus B19 infection, and, in rare cases, PRCA is the initial clinical manifestation of an MDS.

Several causes of acquired PRCA are reviewed here. Transient erythroblastopenia of childhood is an acquired PRCA observed in infants and young children. Affected patients are usually between 6 and 36 months of age and otherwise healthy and present only with the insidious onset of pallor or incidental finding of a normocytic anemia. The degree of anemia is variable but may become severe, and mild neutropenia may also be present. The differential diagnosis includes Diamond-Blackfan anemia (typically MCV is elevated) and parvovirus B19 infection. Although the pathophysiology is not well characterized, most cases appear to be due to an antibody (IgG) directed against erythroblasts. The condition resolves spontaneously within weeks or months with no sequelae. Treatment is supportive, and transfusion is utilized only in symptomatic patients (decreased feeding or weight gain; fatigue).

Parvovirus B19 is a common infection in children, causing erythema infectiosum (ie, fifth disease). More than 75% of adults >50 years old have neutralizing antibodies against this virus. In all infected patients, the virus binds to the blood group P antigen expressed on erythroid progenitors and is cytotoxic to the infected cells. In patients with normal immunity, high-titer parvovirus persists in the blood and marrow for 2 to 3 weeks and is then cleared. Because the normal life span of the RBC is 120 days, infection does not immediately result in a significant decrease in hemoglobin. Alternatively, clinically significant anemia develops in immunosuppressed patients (eg, patients with HIV or organ transplant recipients) whose immune systems are unable to clear the infection or in patients with shortened RBC survival (eg, sickle cell anemia or hereditary spherocytosis). In the latter, the anemic presentation is termed an "aplastic crisis" and often requires transfusion support.

Immunologic causes of acquired PRCA may be idiopathic or secondary to an underlying disease. PRCA develops in approximately 5% of patients with thymoma, and, conversely, thymoma occurs in approximately 10% of patients presenting with PRCA. The response to thymectomy in these cases is variable; a minority of patients achieve complete remission after resection. PRCA may occur in patients with underlying lymphoproliferative disorders (eg, large granular lymphocyte leukemia or chronic lymphocytic leukemia). Because large granular lymphocyte leukemia may be present even in the absence of significant lymphocytosis, it is recommended that patients with idiopathic PRCA undergo lymphocyte immunophenotyping to assess for this malignancy. In patients receiving ABO-mismatched bone marrow transplants, approximately 20% develop a prolonged RBC aplasia due to recipient isohemagglutinins, especially anti-A, against donor RBCs. Generally, the condition improves over time or with the development of graft-versus-host disease. When the anemia is severe or life threatening, treatment with plasma exchange using donor-type plasma and high doses of recombinant human ESAs is effective in some patients.

Many different drugs have been reported to cause PRCA, and drug discontinuation may result in resolution. PRCA rarely has been described from development of anti-EPO antibodies during treatment with recombinant human ESAs, primarily after subcutaneous administration of Eprex (Janssen-Ortho, Toronto, Ontario, Canada), an EPO-α product marketed outside of the United States. The number of ESA-associated PRCA cases peaked in 2001 and

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has since declined following changes in the manufacturing, distribution, storage, and administration of Eprex.

Diagnosis and treatment

Acquired PRCA presents with symptoms related to the severity of the anemia. Apart from pallor, physical examination in acquired primary PRCA often is normal. In acquired secondary PRCA, findings related to the underlying disease such as hepatomegaly, splenomegaly, or lymphadenopathy may be present.

Diagnosis of acquired PRCA is first suggested by finding a normochromic, normocytic, or macrocytic anemia with reticulocytopenia (absolute reticulocyte count of <10,000/μL). The white blood cell and platelet counts are generally normal. Bone marrow biopsy and aspirate establish the diagnosis. In parvovirus B19 infection, the marrow aspirate may show giant pronormoblasts. Routine karyotype and interphase fluorescence in situ hybridization panel for MDS should be included as part of the initial workup to evaluate for an underlying MDS. A careful history and physical exam should be used to guide further diagnostic testing. Additional studies to consider are a CT scan of the chest to evaluate for thymoma, EPO level, and parvovirus B19 DNA testing by polymerase chain reaction.

PRCA caused by parvovirus B19 in immunosuppressed individuals is treated with normal pooled serum IgG, which provides specific antibodies to clear the infection. PRCA associated with thymoma may respond to thymectomy. There does not appear to be any benefit to the removal of a normal thymus in patients with PRCA who do not have a thymoma or thymic hyperplasia identified.

Immunologically mediated PRCA is treated with sequential trials of immunosuppressive therapies (eg, prednisone, cyclosporine, oral cyclophosphamide, mycophenolate mofetil, horse antithymocyte globulin, alemtuzumab, rituximab), which ultimately lead to remission in 60% to 70% of patients. No prospective randomized clinical trial data exist to support the use of one immunosuppressive agent over another. Agent selection is based on the underlying disorder, if identified, and, in idiopathic cases, prednisone or cyclosporine are typical first-line agents. A 3-month trial of each immunosuppressive agent is reasonable to assess for response to therapy. Responsive patients may be treated for 3 to 6 months before immunosuppression is slowly tapered. Many patients relapse after withdrawal of therapy and require a long-term approach to immunosuppression, particularly if an underlying disorder (lymphoproliferative disorder or collagen vascular disease) persists. Causes of death in nonresponding patients include infection, iron overload, or cardiovascular events.

Patients with severe symptomatic anemia are treated with transfusion therapy and face the associated risks of iron overload and alloantibody formation. Supplemental ESAs have been used in certain instances with variable success, such as post-ABO-incompatible bone marrow transplantation.

KEY POINTS

- PRCA is characterized by a severe normochromic, normocytic, or macrocytic anemia with reticulocytopenia (absolute reticulocyte count of <10,000/μL).
- There are 3 pathophysiologic mechanisms of PRCA: immune-mediated, myelodysplasia, and parvovirus B19 infection in an immunocompromised host.
- Transient erythroblastopenia of childhood occurs in otherwise healthy infants and young children and typically resolves over several months. Treatment is supportive.
- Parvovirus B19 infection causes PRCA in all patients infected with the virus, but anemia only manifests in immunosuppressed patients or patients with shortened red cell survival (eg, sickle cell anemia, hereditary spherocytosis).
- PRCA secondary to parvovirus B19 infection is treated with intravenous immunoglobulin.
- In the absence of myelodysplasia or parvovirus B19 infection, PRCA is treated with immunosuppressive agents.

Anemia associated with liver disease

Patients with liver disease often have hematologic abnormalities, with anemia reported in up to 75% of patients with chronic liver disease. The etiology of anemia is multifactorial, reflecting underproduction, blood loss, and increased RBC destruction. In alcoholic liver disease, concomitant folate deficiency may contribute and should be evaluated. Alcohol-induced pancreatitis may also lead to decreased vitamin B_{12} absorption and subsequent deficiency. Ethanol and its metabolites have been shown to directly inhibit erythroid production and may lead to acute or chronic anemia, even in the absence of severe liver disease. EPO production and erythropoiesis are also suppressed by alcohol.

Viral hepatitis may be associated with PRCA. Combination therapy for chronic viral hepatitis may be complicated by clinically significant anemia secondary to ribavirin and/or interferon therapy. Ribavirin-induced hemolysis can be reversed by dose reduction or discontinuation. Interferon may contribute to anemia by inducing bone marrow suppression.

GI blood loss is common in patients with liver disease, especially those with esophageal varices. Shortened RBC survival is also noted in chronic liver disease and at least

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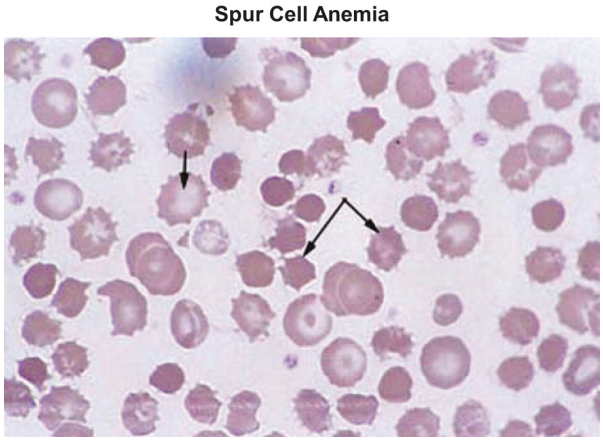

Figure 6-4 Spur cell anemia. Note the acanthocytes (also known as spur cells and indicated with arrows) and target cells.

partially explained by congestive splenomegaly, abnormal erythrocyte metabolism, and alterations in RBC membrane lipids. Peripheral blood film may demonstrate target cells or acanthocytes resulting from changes in cholesterol composition leading to alterations in RBC surface area. Spur cells (Figure 6-4), extreme forms of acanthocytes, may be present in persons with alcoholic liver disease and are associated with a marked hemolytic anemia. In the presence of underlying cirrhosis, spur cell anemia is often irreversible without liver transplantation.

Anemia of liver disease is typically mild to moderate. It may become more severe as cirrhosis, portal hypertension, and splenomegaly develop. Anemia is often macrocytic, but MCV rarely exceeds 115 fL in the absence of megaloblastic changes within the bone marrow. The reticulocyte count is often minimally to moderately elevated but may be suppressed by alcohol or concomitant iron deficiency. More marked reticulocytosis may be seen with hemorrhage or in patients with spur cell anemia. Peripheral blood film shows acanthocytes and target cells as the disease severity increases. Bone marrow cellularity is often increased, and erythroid hyperplasia is observed. Megaloblastosis may be seen in up to 20% of subjects. Treatment of anemia in liver disease is primarily supportive. If present, iron, vitamin B_{12}, and folate deficiencies should be corrected. If persistent hemolysis is noted, folate supplementation should be continued. Alcohol and other toxins should be eliminated, when possible.

Sideroblastic anemias

Sideroblastic anemias are a heterogeneous group of congenital and acquired hematologic disorders characterized by the presence of ringed sideroblasts, which are erythroid precursors with excess mitochondrial iron, in the form of ferritin, that surround (or ring) the nucleus. In both congenital and acquired sideroblastic anemia, formation of ringed sideroblasts is due to either insufficient production of protoporphyrin to utilize the iron delivered to erythroblasts or to defects in mitochondrial function affecting iron pathways and impairing its incorporation into protoporphyrin. X-linked sideroblastic anemia, due to a missense mutation in ALAS2, is the most common. Mutations in SLC25A38 are the most common form of autosomal recessive congenital sideroblastic anemia. In general, congenital sideroblastic anemias are microcytic, and acquired sideroblastic anemias are macrocytic.

Acquired sideroblastic anemias may be clonal (MDS; Chapter 18) or secondary to alcohol, drugs (eg, isoniazid, chloramphenicol, linezolid), or copper deficiency. Sideroblastic anemia associated with alcoholism is common and often found in severely malnourished persons with alcohol use and may be associated with folate deficiency. Pathogenesis is multifactorial and at least partially due to vitamin B_6 deficiency and/or ethanol-induced abnormalities in vitamin B_6 metabolism. Therefore, a trial of vitamin B_6 replacement is reasonable in affected persons. Vitamin B_6 therapy is effective treatment for X-linked congenital sideroblastic anemia as well.

Other underproduction anemias

The underproduction anemias discussed in this section are not typically differentiated by red cell size (MCV).

Anemia associated with pregnancy

Anemia is a common complication of pregnancy. Though both RBC mass and plasma volume increase, RBC mass increases by only 20% to 30% compared to an increase of 40% to 50% in plasma volume, resulting in a normochromic and normocytic anemia. Definitions of pathologic anemia during pregnancy vary. However, the evaluation and workup in pregnant patients should be similar to nonpregnant patients. Anemia of pregnancy can be exacerbated in individuals with sickle cell disease and thalassemia and needs to be carefully monitored and managed.

Iron deficiency during pregnancy is common. A full-term pregnancy requires 1 g of iron: 300 mg for the fetus, 200 mg to replace maternal iron losses, and 500 mg for the expanding maternal RBC mass. Folate requirements also increase during pregnancy. Megaloblastic anemia has been reported, predominantly during the third trimester when maternal folate stores become wasted. Prenatal vitamins containing both iron and folate can help reduce, but not eliminate, these risks. While the majority of screening guidelines for pregnant women focus on anemia screening, screening with a serum ferritin identifies the presence of

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iron deficiency with or without anemia, which can be treated with iron supplementation. Vitamin B_{12} deficiency rarely occurs during pregnancy. There are reports of idiopathic acquired aplastic anemia patients experiencing a worsening in their cytopenias or even relapse during pregnancy. Further information on anemia in pregnancy can be found in Chapter 3.

KEY POINTS

- Anemia in pregnancy is due in part to an imbalance between expansion of plasma volume and the RBC mass.
- Iron deficiency and folate deficiency are important causes of anemia in pregnancy, with iron deficiency being the most common.
- The evaluation of anemia in pregnancy should be similar to the evaluation of anemia in nonpregnant individuals.

Anemia of cancer

Anemia in cancer patients is common, and its prevalence may exceed 90% in patients with advanced disease receiving chemotherapy. Its presence and severity is dependent on many variables, including cancer type and stage, as well as past and current therapy. Approximately two-thirds of patients with cancer are anemic at diagnosis or become anemic (hemoglobin <12.0 g/dL) during the course of their treatment. The lowest hemoglobin levels are typically seen in patients with advanced disease and significantly compromised performance status. The mechanisms underlying anemia of malignancy are complex, with numerous factors contributing to its development. Cytokine-mediated changes cause both a relative decrease in EPO production and a decrease in EPO responsiveness of erythroid precursors. As in AOCD, cytokines promote hepcidin production resulting in iron-restricted erythropoiesis. Hemoglobin concentrations in cancer patients inversely correlate with inflammatory markers, serum hepcidin, serum ferritin, EPO, and reactive oxygen species. Additional factors contributing to anemia of cancer include bone marrow infiltration, treatment effects of chemotherapy and radiotherapy, blood loss, autoimmune and microangiopathic hemolysis, and nutritional deficiencies. See Chapter 4 for additional details on the use of ESAs in malignancy.

KEY POINT

- Anemia is frequent in cancer patients and leads to decreased quality of life.

Myelophthisic anemia

Myelophthisic anemia is a normochromic, normocytic anemia that occurs when normal marrow space is infiltrated and replaced by abnormal or nonhematopoietic cells. The term *myelophthisic* is not commonly used in clinical practice, and more often this anemia is referred to descriptively as a marrow infiltrative process. Causes include tumors, granulomatous disorders, bone marrow fibrosis (due to a primary hematologic or nonhematopoietic disorder), and lipid storage diseases; all causes may induce secondary marrow fibrosis. The peripheral blood film in myelophthisic anemia shows a leukoerythroblastic process with teardrop-shaped and nucleated RBCs, immature leukocytes, and occasional myelobasts. Rarely, carcinocythemia, defined as cancer cells within the circulating blood, is seen. Bone marrow biopsy may show frank tumor cells, Gaucher disease, or other infiltrating disorders, as well as marked marrow fibrosis. These conditions may be accompanied by extramedullary hematopoiesis resulting in organomegaly due to marrow elements in the spleen, liver, or other affected tissues. T1-weighted MRI may demonstrate areas of abnormal signal, consistent with marrow infiltration. Treatment is directed at the underlying disease.

During infancy, anemia secondary to marrow fibrosis may be seen in the setting of osteopetrosis or marble bone disease, which is caused by failure of osteoclast development or function. These conditions vary in their severity, but infants affected with the autosomal recessive form present within the first few months of life with pancytopenia, hepatosplenomegaly, cranial nerve palsies, and changes in calcium levels. Mutations in at least 10 genes have been identified in patients with osteopetrosis, accounting for 70% of cases. Severe cases are treated by bone marrow transplantation.

Anemia associated with heart failure

Anemia is common in patients with heart failure and is associated with worse symptomatology and long term outcomes. Etiologies for anemia are multifactorial and include elevation in proinflammatory cytokines, including hepcidin, chronic renal disease or dysfunction, iron deficiency, and, less commonly, vitamin B12 or folate deficiencies. Iron deficiency alone—either absolute or functional—is independently associated with worse outcomes in these patients.

Heart failure patients with chronic anemia should undergo a complete evaluation for causes of anemia, including the assessment of iron parameters. A large trial of ESAs was associated with increased adverse effects and did not demonstrate long-term improvements and is therefore

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not typically recommended. A large placebo-controlled trial of oral iron demonstrated no significant improvement in iron parameters. In contrast, several large studies of IV iron therapy have demonstrated improvements in both subjective (patient-centered) and objective heart failure measures. Thus, in patients with confirmed iron deficiency, IV iron should be considered, though not continued indefinitely.

KEY POINTS

- Anemia is common in patients with heart failure and often multifactorial due to a combination of anemia of chronic disease, absolute or functional iron deficiency, concomitant renal disease, and/or other comorbid conditions.
- In contrast to ESAs, trials of IV iron have demonstrated improvement in both objective and patient-reported measures in patients with concomitant heart failure and iron deficiency.

Copper deficiency anemia

Copper is an essential trace element that plays a critical role in numerous physiologic processes, including proliferation and differentiation. Copper deficiency is rare in humans. When present, it is typically due to either inadequate intake (eg, total parenteral nutrition without copper supplementation) or absorption (eg, postbariatric surgery, celiac disease, enteral nutrition received via a gastro-jejunal tube, excessive zinc intake, congenital defect in copper transport, Menkes disease). Copper deficiency may cause anemia, neutropenia, and, less commonly, thrombocytopenia. A review of 40 patients with copper deficiency unrelated to Wilson disease found that 25%-35% were postbariatric surgery or gastric resection; an additional 30% had no identifiable cause. The red cell size in anemia due to copper deficiency has been reported variably as microcytic, normocytic, or macrocytic. It can mimic an acquired MDS, manifesting with a macrocytic anemia, neutropenia, and diverse marrow morphology including ringed sideroblasts, dyserythropoiesis, dysmyelopoiesis, and cytoplasmic vacuolization of erythroid and myeloid precursors, as well as hemosiderin-laden plasma cells. In addition to the hematologic manifestations, copper deficiency can cause neurologic symptoms resembling the subacute combined degeneration seen in patients with vitamin B_{12} deficiency.

The mechanism by which copper deficiency results in hematologic changes is unknown. Copper is a cofactor for various redox enzymes, including hephaestin and ceruloplasmin, which are required to convert ferrous iron to its ferric form, a step necessary for the transport of iron by transferrin in the intestine and liver, respectively. Cytochrome *c* oxidase also requires copper as a cofactor. A decrease in this enzyme's activity may contribute to the development of ringed sideroblasts identified in some cases of copper deficiency. Measurement of serum copper level diagnoses copper deficiency; ceruloplasmin level can also be assessed but lacks specificity.

Anemia associated with endocrine disorders

In general, the anemia associated with endocrine disorders is mild and the symptomatology overshadowed by the clinical effects of the specific hormone deficiency. In some cases, the anemia may be physiologic due to the decreased oxygen requirements accompanying the hormone deficiency.

Deficiencies in hormones produced by the anterior lobe of the pituitary gland (thyroid hormone, androgens, or cortisol), which modulate EPO production, are associated with a mild normochromic, normocytic anemia. The bone marrow is usually hypoplastic and resembles that seen in other marrow failure states. The anemia improves after initiation of appropriate hormone replacement to address the underlying deficiency.

Patients with primary hypothyroidism may be anemic due to an absence of EPO-stimulated erythroid colony formation from lack of triiodothyronine, thyroxine, and reverse triiodothyronine. The anemia is usually normochromic and normocytic, and the hemoglobin concentration typically does not fall below 8 g/dL. Macrocytosis may be present in patients with autoimmune hypothyroidism, particularly if there is coexistent vitamin B_{12} or folate deficiency, or hemolysis. Conversely, microcytosis can occur in women with concomitant iron deficiency from abnormal uterine bleeding, which can occur in myxedema. There is a well-recognized association between autoimmune thyroid disease and PA, so patients with either disorder should be screened for the other. Response to thyroid replacement is typically slow, and it may take months before the anemia resolves. Concurrent administration of thyroid replacement and oral iron therapy can affect absorption. Therefore, stable and consistent dosing should be maintained or intravenous iron therapy should be considered. Microcytic anemia in patients with hyperthyroidism is also described and often corrects when patients become euthyroid.

Hypogonadism usually results in a decrease of 1 to 2 g/dL in hemoglobin concentration due to androgens' role in stimulating EPO production and increasing

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its effects on the developing erythron. This mechanism explains why men have higher hemoglobin concentrations compared to age-matched women. Men treated with antiandrogen therapy for prostate cancer therefore typically have a decrease in hemoglobin concentration by 1 to 2 g/dL.

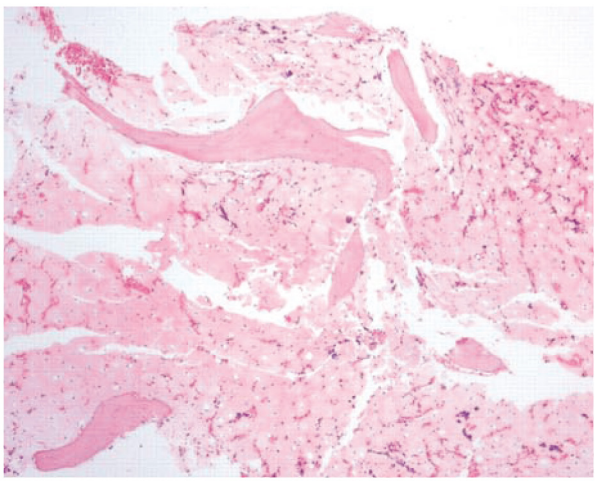
A normochromic, normocytic anemia responsive to ESAs or glucocorticoids may be seen in patients with Addison disease. These patients develop a mild decrease in RBC mass that may be unrecognized due to a concomitant decrease in plasma volume, resulting in a normal hemoglobin concentration. When glucocorticoid therapy replacement is initiated, plasma volume is restored, and the anemia is unmasked. Androgens may be useful to correct the anemia of myelofibrosis and myeloid metaplasia.

Anemia presents earlier and is more severe in patients with diabetic nephropathy compared to patients with other causes of renal failure. The exact mechanism for this finding remains unclear.

Anemia from malnutrition or anorexia nervosa

Prolonged starvation can lead to a normochromic, normocytic anemia, and bone marrow aspirates from such patients are often hypocellular. Rarely, patients with severe starvation or anorexia nervosa can have gelatinous transformation of the marrow with few marrow-derived cells seen histologically (Figure 6-5).

Figure 6-5 Anorexia nervosa. A marrow biopsy specimen is shown, illustrating almost complete replacement of the marrow by hyaluronic acid extracellular matrix material. Hematopoietic elements and fat cells are markedly decreased. Hematoxylin and eosin stain; magnification ×4.



Anemia in older persons

Approximately 11% of men and 10% of women over age 65 years are anemic (defined as hemoglobin concentration <13 g/dL for men; <12 g/dL for women). Prevalence rates are higher in older African Americans and increase with age (30% in patients over 80 years; 37% in those over 90 years). In this population, anemia is an independent risk factor for cognitive decline and is associated with decreased bone density, muscle strength, and physical performance. The presence of anemia, with or without other comorbid diseases, is associated with increased hospitalization, morbidity, and mortality.

Analysis of NHANES III data found that approximately two-thirds of anemia cases were attributable to iron deficiency, other nutritional deficiencies, chronic inflammatory illnesses, and/or renal insufficiency. Roughly 34% of cases were unexplained but are likely due to a variety of underappreciated etiologies such as underlying renal disease, low EPO, low androgen, and/or alterations in bone marrow stem cells and cellularity.

Due to comorbid conditions typically present in the older population, it is difficult to reach consensus on goal hemoglobin concentration levels to target for supportive blood transfusion therapy. However, many attempt to maintain a hemoglobin of 9 to 10 g/dL. As anemia in an older patient is often multifactorial, a thorough clinical and laboratory evaluation is justified to identify those causes of anemia that are amenable to therapy. A reasonable approach to evaluation is given in Table 6-10.

Table 6-10 Practical approach for the evaluation of anemia in older patients

Initial assessment
1. Anemia-oriented clinical history and physical examination, with emphasis on comorbid conditions and medications
2. CBC/differential/platelet, absolute reticulocyte count, smear review
3. Iron panel (Fe, TIBC, ferritin)
4. Serum cobalamin and folate levels, RBC folate (methylmalonic acid, serum homocysteine)
5. Chemistry panel (including calculated creatinine clearance)
6. Thyroid function (TSH)
Additional assessment, if indicated
1. Serum testosterone
2. Serum EPO
3. Laboratory assessment of inflammation (ESR, C-reactive protein)
4. Bone marrow aspiration and biopsy, cytogenetics

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TSH, thyroid-stimulating hormone.

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KEY POINTS

- Anemia is common in older patients and often multifactorial.
- In two-thirds of older patients, the anemia is caused by nutritional deficiency or AOCD. It is unexplained in one-third of patients.
- Functional impairment and increased morbidity and mortality have been demonstrated in anemic older patients.
- Transfusion practice to maintain hemoglobin concentration thresholds of 9 to 10 g/dL for the older population may be prudent.

Anemia associated with HIV infection

Anemia is the most common hematologic abnormality associated with HIV infection, and its prevalence increases with HIV disease progression. Anemia is associated independently with decreased survival and decreased quality of life in HIV-infected patients. Anemia in this population is multifactorial, and the most likely etiologies depend on both the stage of the infection and the medications the patient is receiving.

The underlying inflammatory pathways of HIV contribute to the pathophysiology of anemia. In addition, antiretroviral therapies as well as drugs used for prophylaxis or treatment of opportunistic infections, may result in bone marrow suppression. Zidovudine (AZT) is the leading cause of therapy-associated anemia due to bone marrow suppression among patients with HIV and was reported in up to 25% of patients in phase 1 trials. Macrocytosis is also common in patients receiving AZT. Rarely, tenofovir is associated with anemia or other hematologic side effects. Macrocytosis has been reported in stavudine and lamivudine. Trimethoprim-sulfamethoxazole, ganciclovir, valganciclovir, and Amphotericin B can also result in bone marrow suppression. Infections commonly seen in HIV patients and associated with anemia include *Mycobacterium avium* complex, tuberculosis, histoplasmosis, cytomegalovirus, Epstein-Barr virus, and human parvovirus (see the section "Acquired pure red cell aplasia"). Malignant disorders, mainly non-Hodgkin lymphoma, can infiltrate the bone marrow and cause anemia. Nutritional deficiencies, including vitamin B_{12}, folate, and iron, are common in HIV patients and are related to blood loss, malabsorption, and overall poor nutrition. These patients are also at risk for hemolysis, including microangiopathic hemolysis, antibody-mediated mechanisms, and drug-induced mechanisms, especially in patients with glucose-6-phosphate dehydrogenase deficiency. Hypogonadism is a frequent finding in patients with advanced HIV and is associated with a mild anemia as described previously. The HIV virus itself also directly infects bone marrow cells and may interfere with hematopoiesis.

The use of highly active antiretroviral therapy (HAART) has been shown to reduce the prevalence of anemia in several population studies, even when zidovudine remains within the regimen. In addition to HAART, the management of anemia in HIV patients should include correction of nutritional deficiencies and appropriate prevention and treatment of infections. ESAs reduce transfusion requirements in HIV patients with baseline EPO levels of <500 mU/mL, in whom nutritional deficiencies and other causes have been corrected.

KEY POINTS

- HIV-related anemia is common and independently associated with decreased survival.
- Anemia in HIV is multifactorial and may reflect viral infection, malignancy, malnutrition, and medication effect.
- In patients treated with zidovudine, the finding of macrocytosis is more common than anemia.
- HAART reduces the incidence and degree of anemia in HIV- infected patients.

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